TAYSHA GENE THERAPIES

# TSHA-101 in GM2 Gangliosidosis Program Update

**January 27, 2022**

# Legal disclosure

## FORWARD LOOKING STATEMENTS

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements are subject to a number of risks, uncertainties and assumptions. Risks regarding our business are described in detail in our Securities and Exchange Commission filings, including in our Annual Report on Form 10-K for the year ended December 31, 2020, and our Quarterly Report on Form 10-Q for the quarter ended September 30, 2021. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements contained in this presentation reflect our current views with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law.

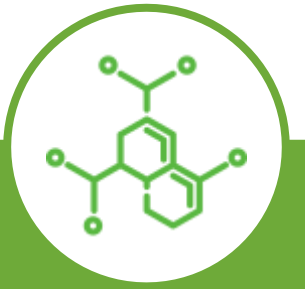
This presentation includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties as well as our own estimates of potential market opportunities. All of the market data used in this prospectus involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions.

# TSHA-101 represents important firsts for the field of gene therapy

TSHA-101
GM2

First bicistronic gene therapy in clinical development

First vector approach to deliver 2 genes in a single capsid for both Sandhoff and Tay-Sachs diseases



First treatment to demonstrate normal levels of β-Hexosaminidase A enzyme activity

# Positive initial biomarker data for TSHA-101, the first bicistronic gene therapy in history

TSHA-101
GM2

## Safety

- Preliminary data suggest TSHA-101 was well-tolerated with no significant drug-related events

## β-Hexosaminidase A enzyme activity

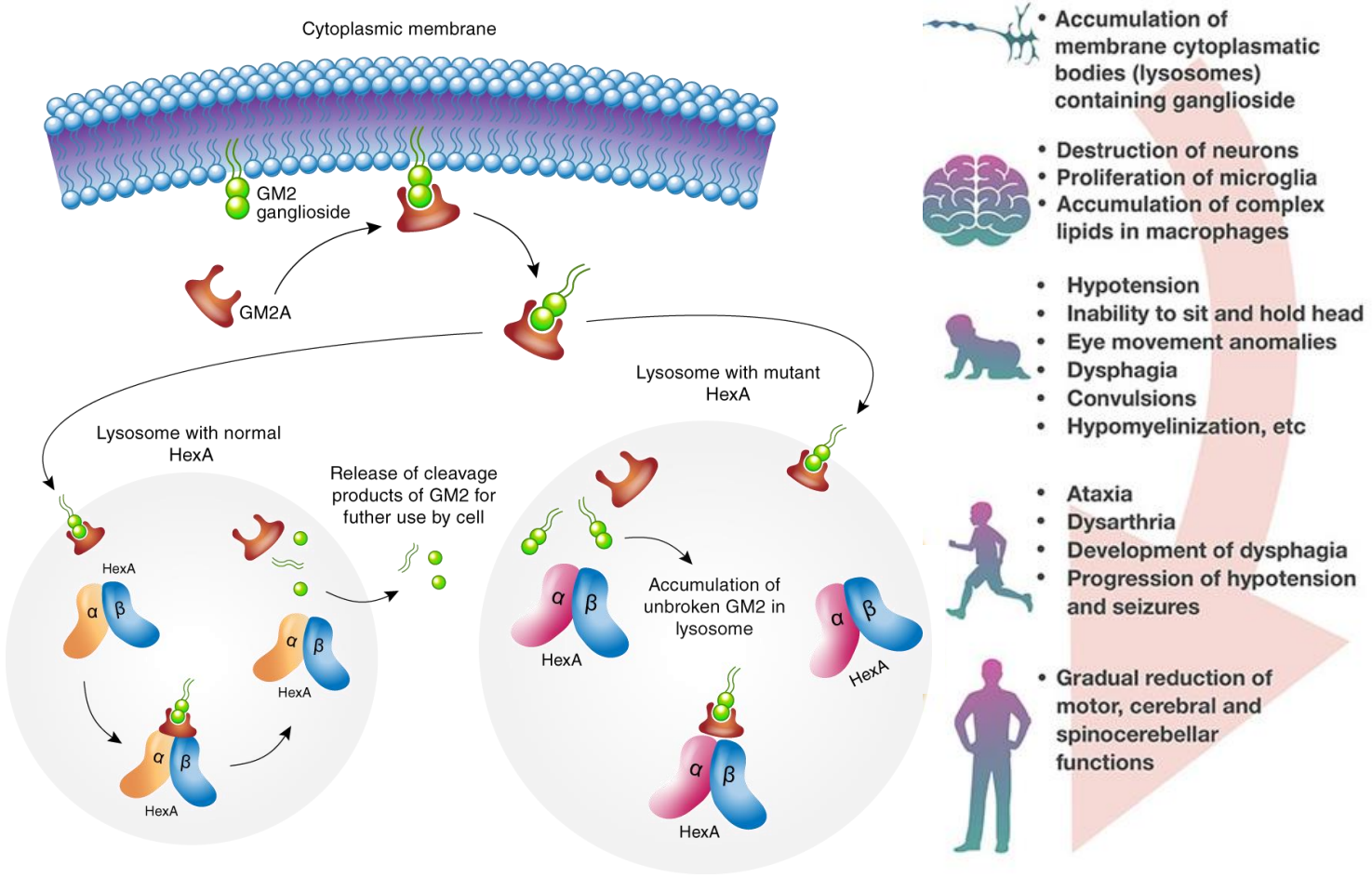
- Restoration and normalization of serum β-Hexosaminidase A (Hex A) enzyme activity at Month 1 and 3
- Patient 1 (Sandhoff) achieved 190% and 288% of normal serum Hex A enzyme activity, representing 38-fold and 58-fold above the 5% enzyme activity level of asymptomatic patients identified by natural history data at Month 1 and 3
- Patient 2 (Tay-Sachs) achieved 25% of normal serum Hex A enzyme activity, representing 5-fold above the 5% enzyme activity level of asymptomatic patients identified by natural history data at Month 1

## GM2 to GM3 Metabolic Pathway

- Confirmatory evidence of pathway restoration with increased levels of GM3 ganglioside in CSF
- Patient 1 (Sandhoff) demonstrated a greater rate of increase in GM3 ganglioside versus GM2 ganglioside

# GM2 gangliosidosis is a severe neurodegenerative disease

- GM2 gangliosidosis results from a deficiency in the β-hexosaminidase A (Hex A) enzyme
- Hex A is comprised of 2 subunits encoded by the alpha-subunit, HEXA, coded for by the *HEXA* gene, and the beta-subunit, HEXB, coded for the *HEXB* gene
- Mutations of the *HEXA* gene cause Tay-Sachs disease (TSD) while mutations of the *HEXB* gene cause Sandhoff disease (SD)
- Estimated prevalence is 500 patients (US+EU)



# GM2 gangliosidosis is comprised of two separate diseases: Tay-Sachs and Sandhoff disease

TSHA-101
GM2

- Genetic mutations resulting in deficient activity of β-Hexosaminidase A enzyme lead to the development of GM2 gangliosidosis which includes Sandhoff disease and Tay-Sachs disease
- Both forms of GM2 gangliosidosis cause progressive deterioration of nerve cells, are clinically indistinguishable and ultimately fatal
- There are no current treatments for GM2 gangliosidosis

## Tay-Sachs Disease

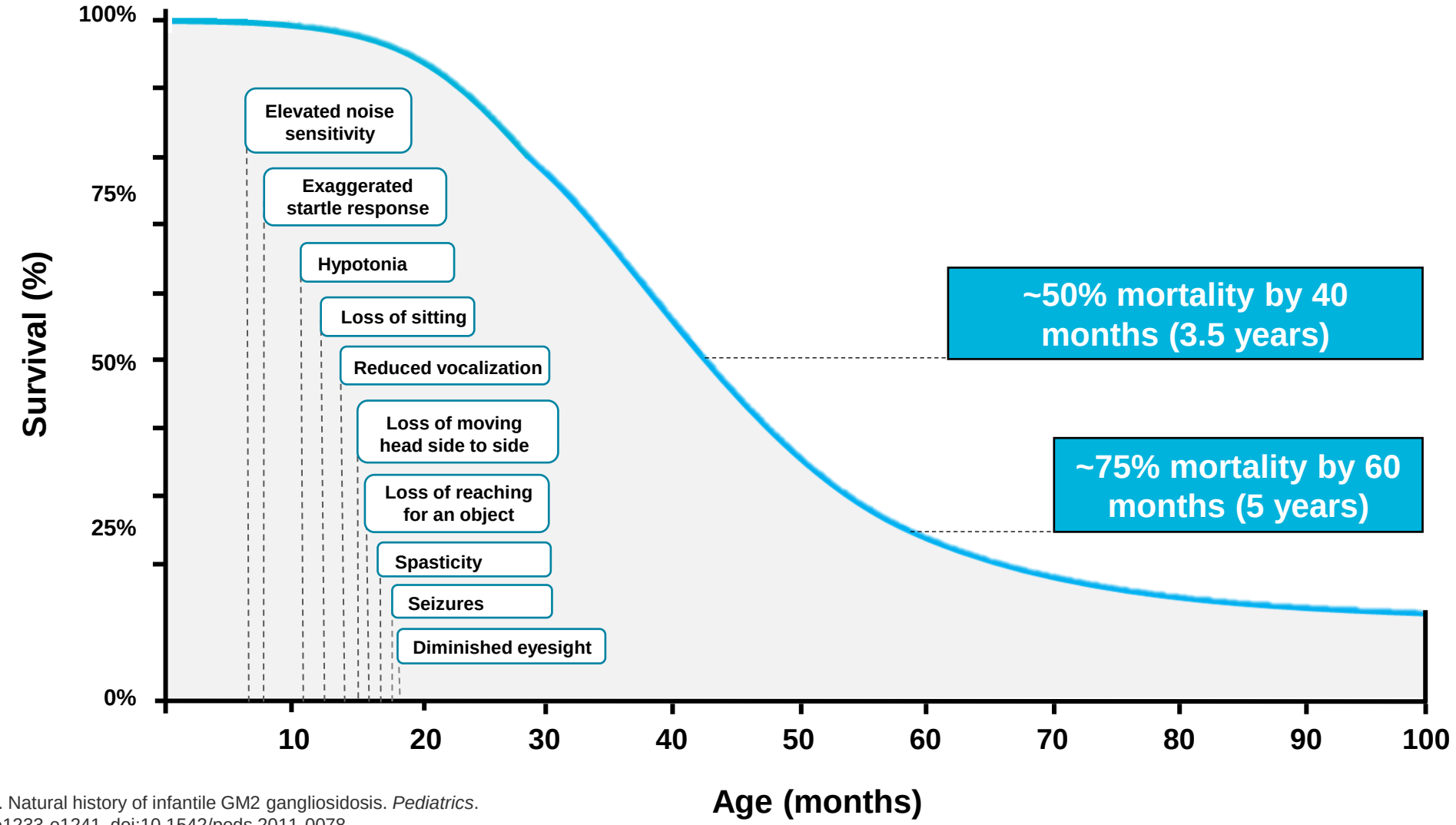
- Tay-Sachs disease is an inherited metabolic disease caused by harmful lipid accumulation in various cells and tissues in the body and results from a deficiency in the α-subunit of β-hexosaminidase caused by a gene mutation on chromosome 15, specifically 15q23-q24
- Mutations of the *HEXA* gene cause Tay-Sachs disease (TSD)
- Death generally occurs around 4 years of age
- No current treatments

## Sandhoff Disease

- Sandhoff disease is a rare, inherited lipid storage disorder and a severe form of Tay-Sachs disease that results from a deficiency in the β-subunit of β-hexosaminidase caused by a gene mutation on chromosome 5, specifically 5q13
- More severe form of GM2 gangliosidosis
- Mutations of the *HEXB* gene cause Sandhoff disease (SD)
- Death usually occurs by 3 years of age
- No current treatments

# Natural history clinical progression of infantile GM2 gangliosidosis

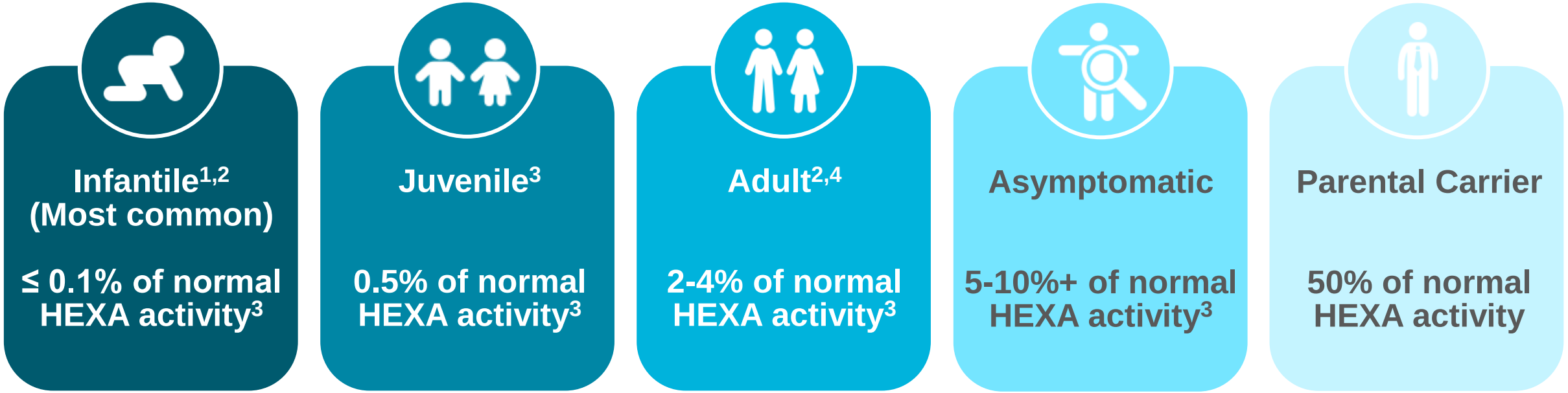





Bley AE, et al. Natural history of infantile GM2 gangliosidosis. *Pediatrics*. 2011;128(5):e1233-e1241. doi:10.1542/peds.2011-0078

# Serum β-Hexosaminidase A enzyme (Hex A) activity correlates with disease severity

TSHA-101
GM2

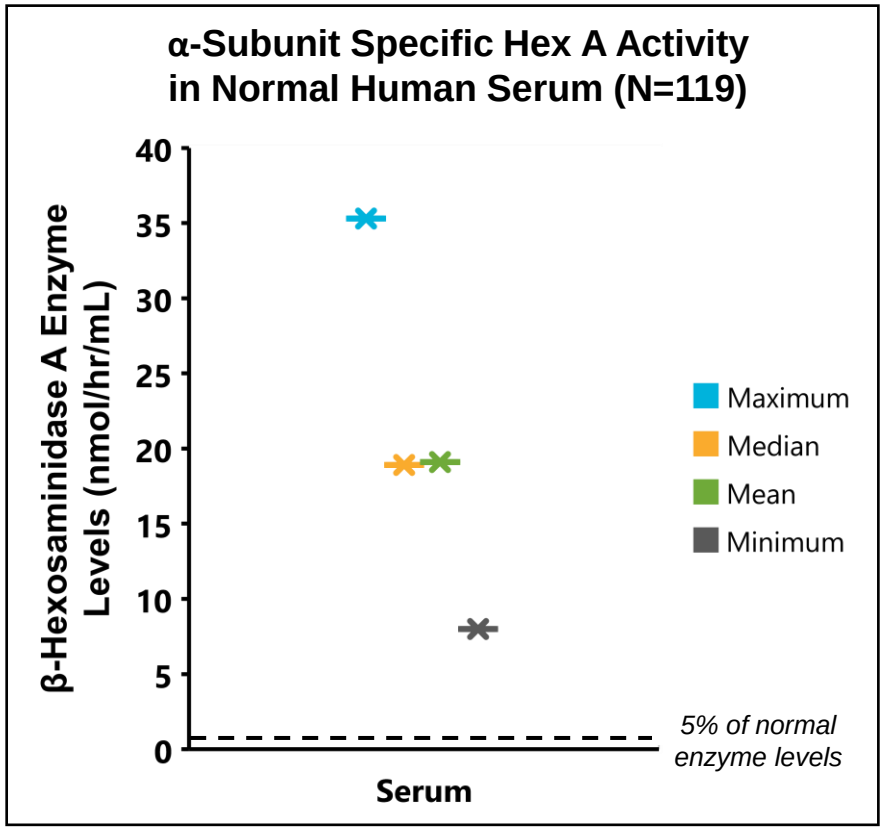



***5% or above β-hexosaminidase A enzyme activity in the serum correlates with asymptomatic patients based on natural history***


1. Bley et al. *Pediatrics*. 2011; 128(5):1233-1241.
2. Cachon-Gonzalez et al. *Curr Gene Ther*. 2018; 18(2):68-89.
3. Mahuran, *Biochim Biophys Acta.* 1999; 1455(2-3):105-38.
4. Neudorfer et al. *Genet Med.* 2005; 7(2):119-23.

# Robust scientific approach to β-Hexosaminidase A enzyme activity assay development

- 120 samples of normal Hex A enzyme levels were obtained from commercial vendor
- Activities were measured at a contract lab (PPD) and in Taysha's internal nonclinical lab
- 5% of normal Hex A enzyme activity equates to 0.4 nmol/hr/mL
- 5% of normal Hex A enzyme activity correlates with asymptomatic patients with GM2 gangliosidosis based on natural history

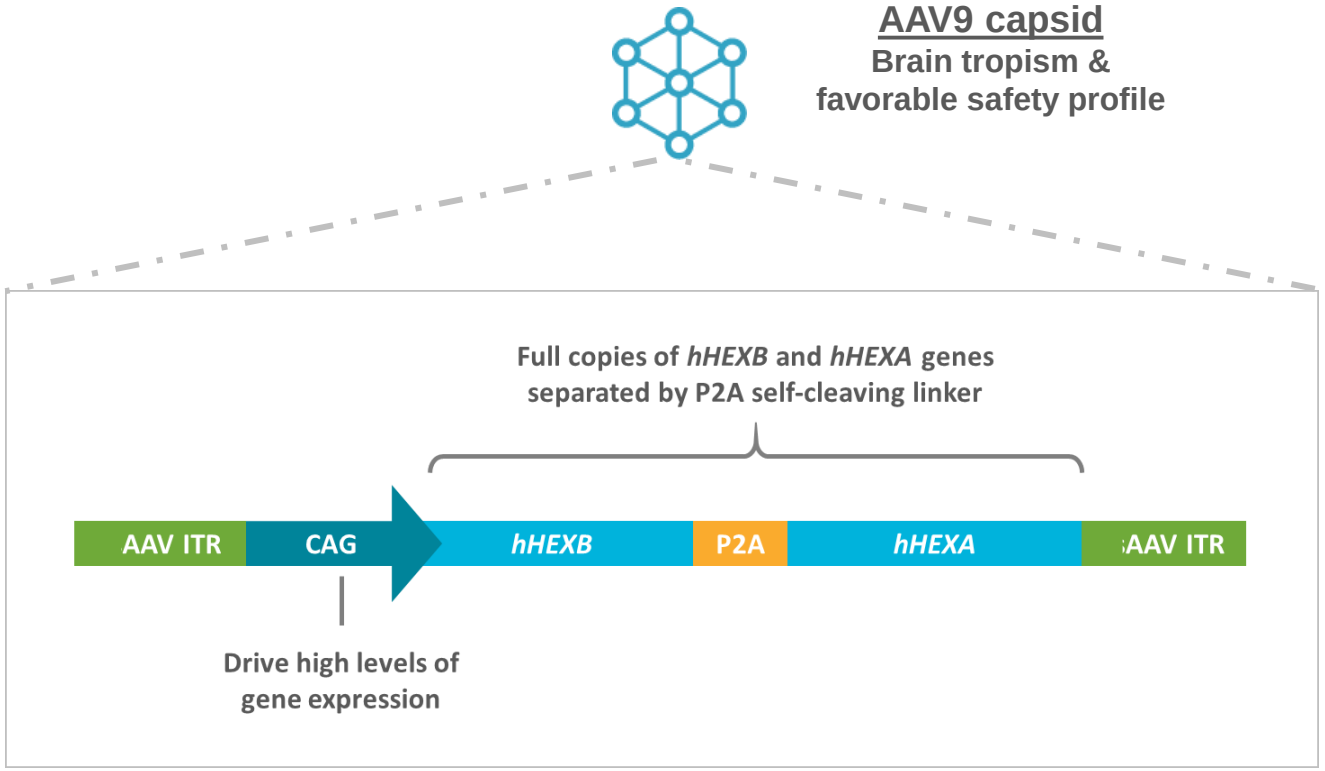



| Statistic | α-Subunit Specific Hex Activity (nmol/hr/mL) |
|---|---|
| **Maximum** | 35.3 |
| **Median** | 18.9 |
| **Mean** | 19.1 |
| **Minimum** | 8.0 |

# Novel bicistronic vector design allows consistent expression of *HEXA* and *HEXB* genes



- *HEXA* and *HEXB* genes are required to produce the subunits of the β-hexosaminidase A enzyme
- The novel bicistronic vector design enables 1:1 expression of the α-subunit, *HEXA,* and the β-subunit, *HEXB,* under the control of a single promoter with a P2A-self-cleaving linker
- Bicistronic vector allows for delivery of two genes in a single construct



# Phase 1/2 adaptive trial for TSHA-101 in GM2 gangliosidosis

TSHA-101
GM2

## Goals and Targets of Trial

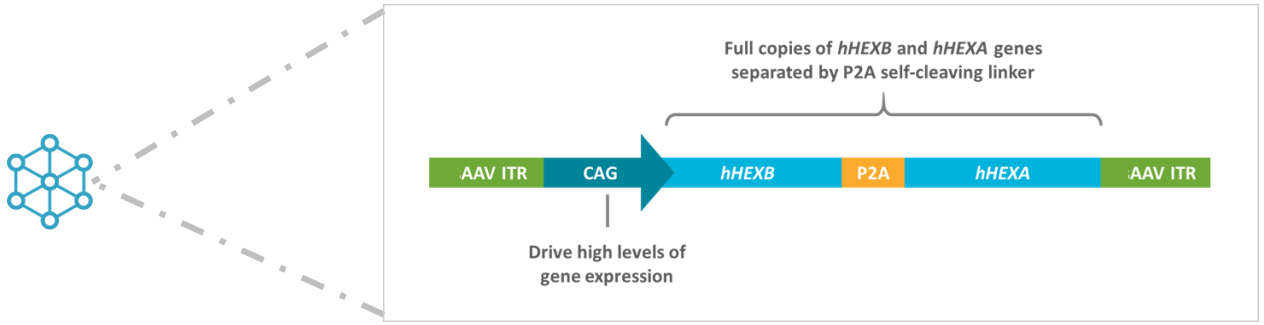
### Goals

- **Primary** – Safety: clinical and laboratory assessments
- **Secondary** – Efficacy: pathologic, physiologic, functional and clinical markers

### Target Recruitment

- 4 subjects; both Sandhoff and Tay-Sachs patients
- Age younger than or equal to 15 months at time of enrollment

## Product Details and Dose Cohorts



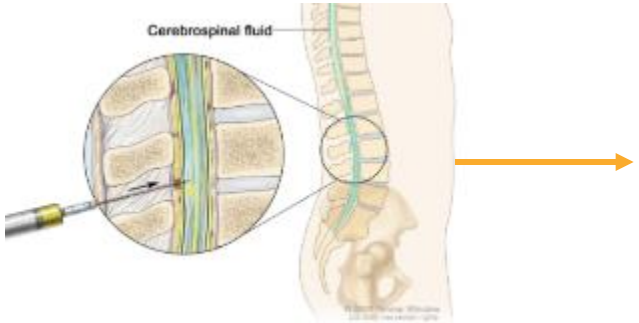

### Dose Cohorts

- 5 x $10^{14}$ total vg (n=4)

## Route and Method of Administration

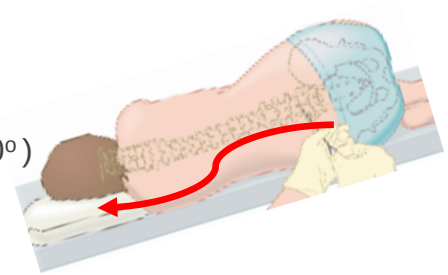
### Administration

- Lumbar Intrathecal Infusion (IT)
- Amount and rate: 1 mL/min for total of 10-12 mL
- Immunosuppression regimen of prednisolone and sirolimus




### Technique to Improve Transduction

- Trendelenburg position (15-30º)
- Following IT injection, for 15 minutes post infusion



# Key study inclusion criteria

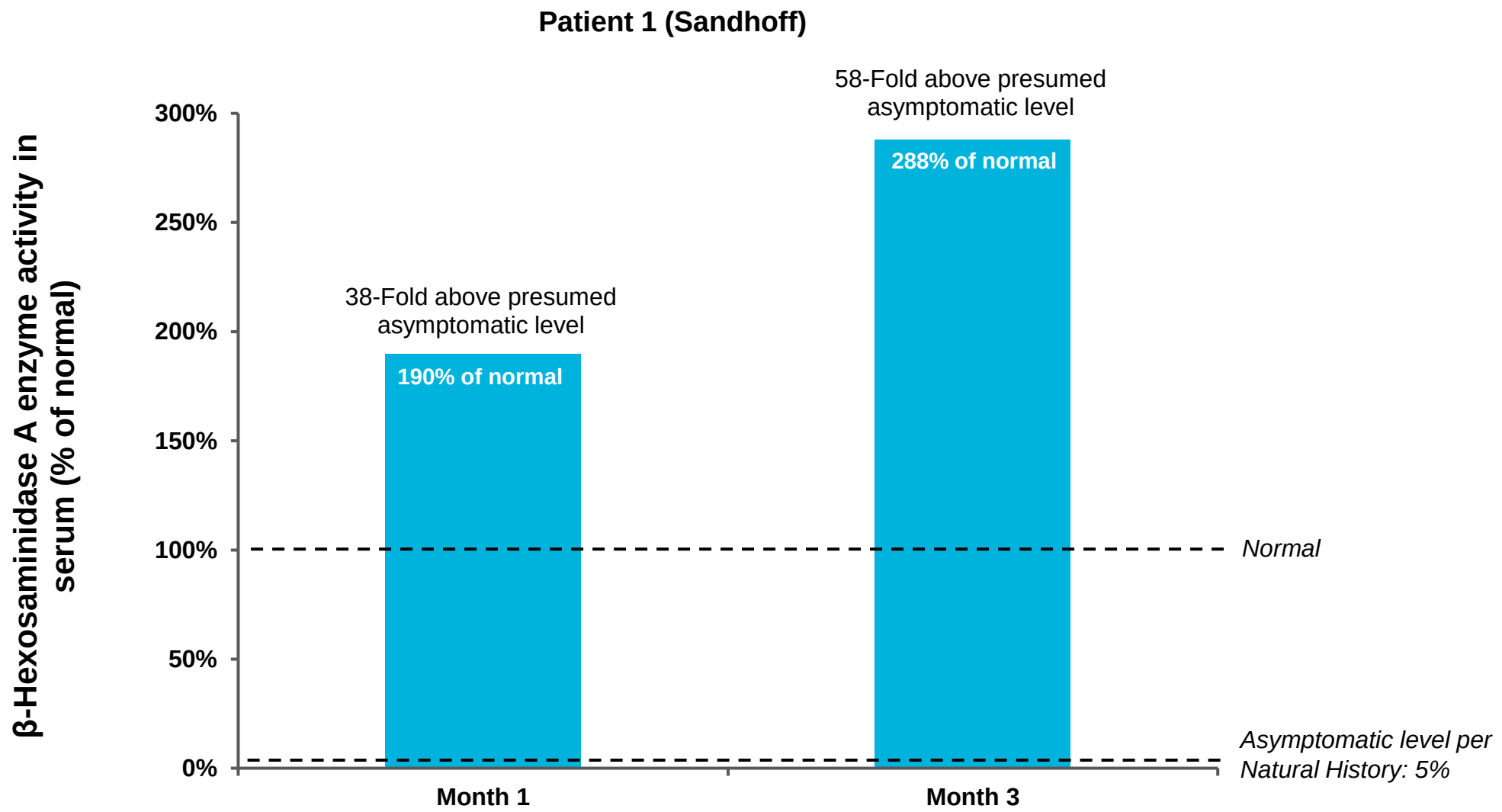
| | Infantile GM2 gangliosidosis |
|---|---|
| **Age** | ≤ 15 months by the time of dosing |
| **Disease Confirmation** | Biochemical confirmation of reduced hexosaminidase enzyme activity in serum (infantile form)<br>*AND*<br>Molecular confirmation of infantile form |
| **Onset of Symptoms** | Symptomatic participants > 6 months old (i.e., clinically infantile form): Molecular demonstration of infantile pathogenic genetic mutation in HEXA or HEXB<br>*OR*<br>Pre-symptomatic participants ≤ 6 months old: Family history of genetically confirmed infantile GM2 gangliosidosis and presence of familial mutations |

# Baseline characteristics of evaluable patients

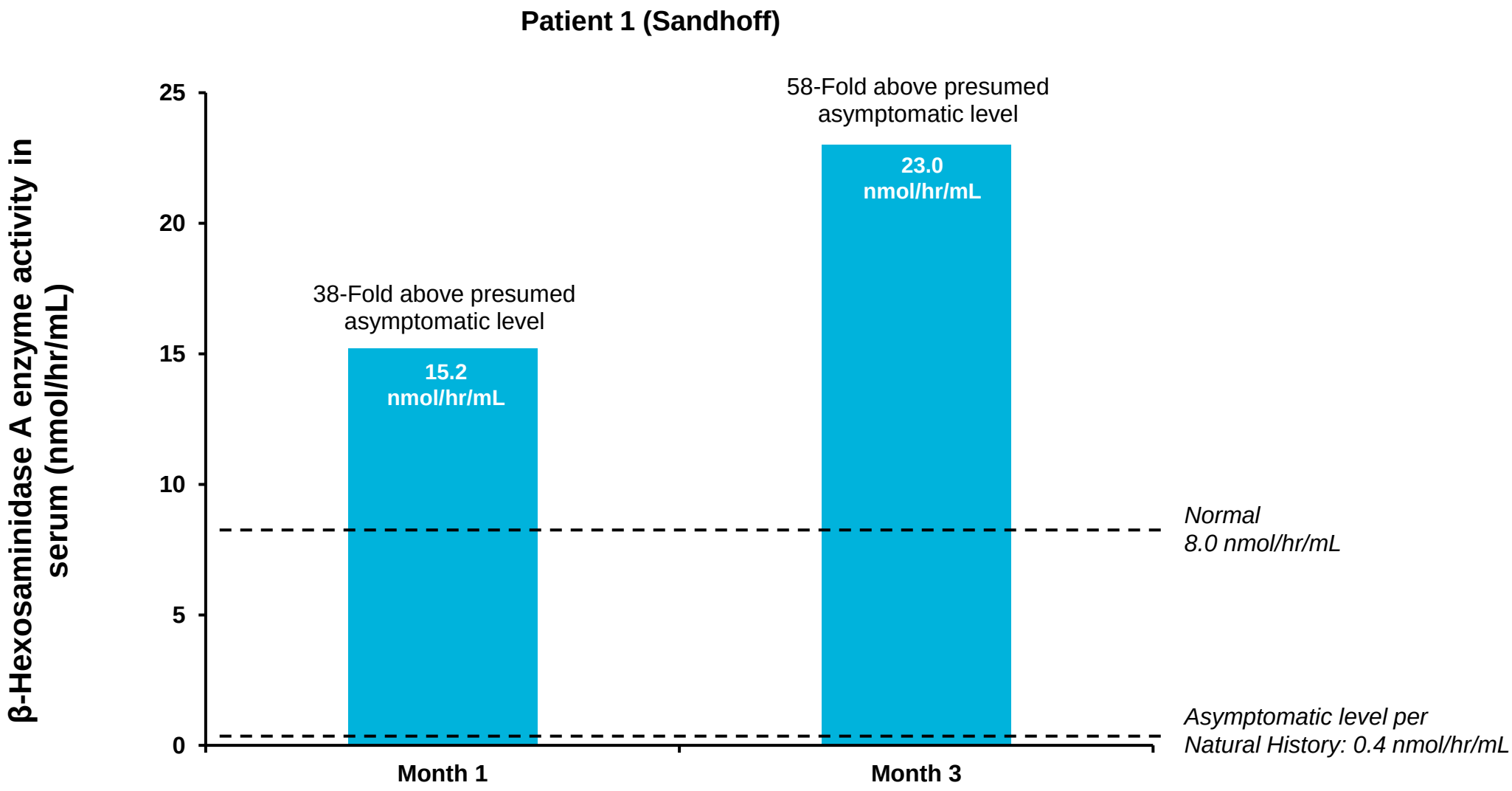
| Characteristics | Patient 1 | Patient 2 |
|---|---|---|
| **Gender** | Male | Female |
| **Age at disease onset** | 6 months | 12 months |
| **Age at time of consent** | 13 months | 13 months |
| **Disease state** | Sandhoff disease | Tay-Sachs disease |
| **Mutation** | HEXB - Homozygous for c.445+1 G>A | Proband biallelic for HEXA, c.1073+1 G>A and c.1330+1 G>A |
| **Clinical Features at Onset** | • Regression of milestones<br>• Visual problems<br>• Loss of motor skills<br>• Hearing loss | • Missed milestones and regression of milestones<br>• Fine motor problems<br>• Seizures<br>• Loss of motor skills<br>• Hearing loss |
| **Immunosuppression** | • Prednisolone at 11 mg (1 mg/kg/d) QD<br>• Sirolimus at 0.8mg/$m^2$ BID starting | • Prednisolone at 8.5 mg (1 mg/kg/d) QD<br>• Sirolimus at 0.33 mg/$m^2$ BID |
| **Concomitant Medications** | • PEG 3350<br>• Topiramate suspension | • Tylenol |
| **Past Medical History** | • Dysphasia<br>• Hypercholesterolemia<br>• Hearing loss<br>• High myopic astigmatism bilateral<br>• LDH elevation<br>• AST elevation | • Hearing loss<br>• Dysphagia<br>• LDH elevation<br>• AST elevation |

# Patient 1 (Sandhoff) experienced Hex A enzyme activity 288% above normal at Month 3



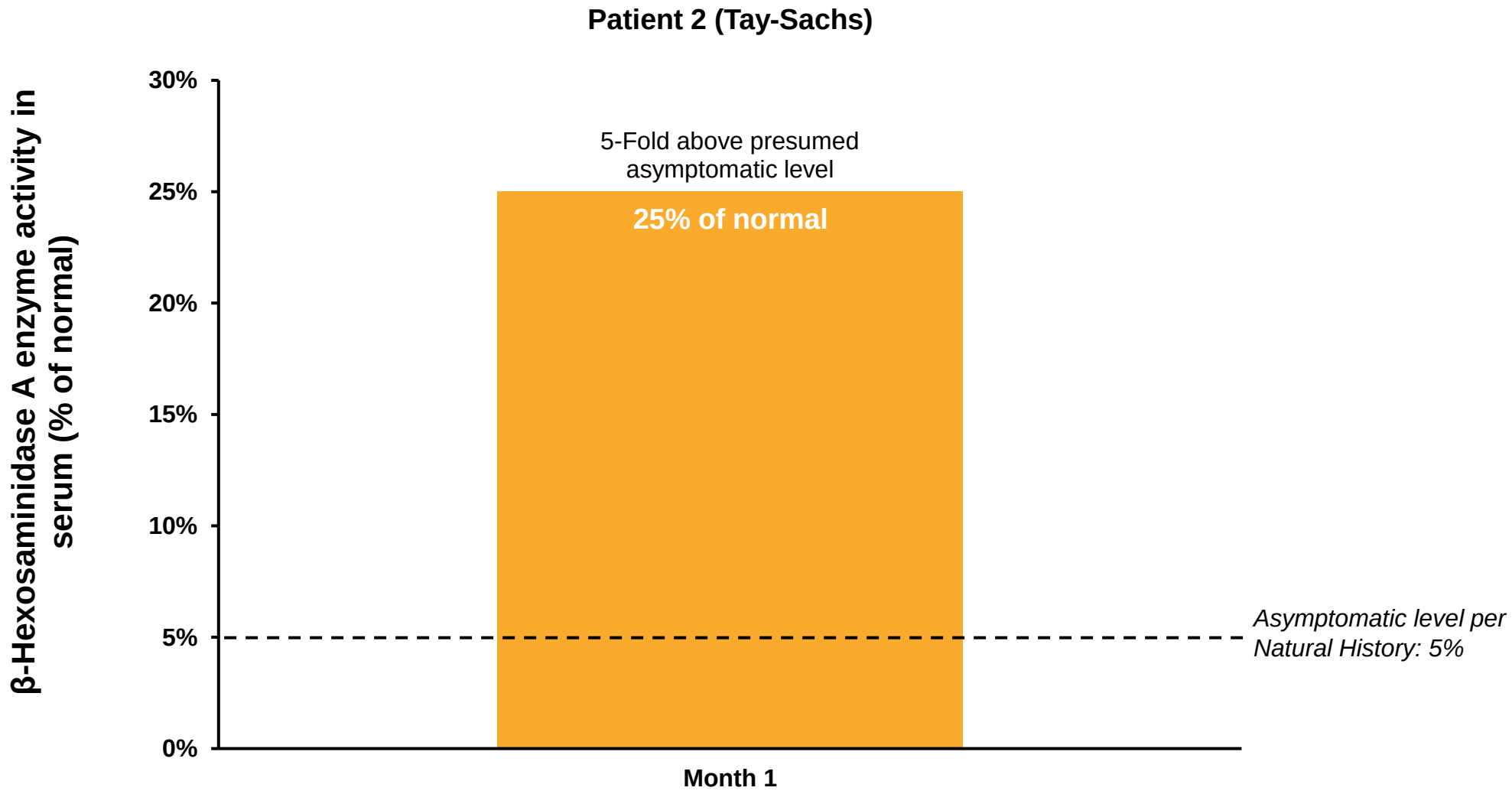


# Patient 1 (Sandhoff) experienced Hex A enzyme activity 58-fold above presumed asymptomatic level at Month 3



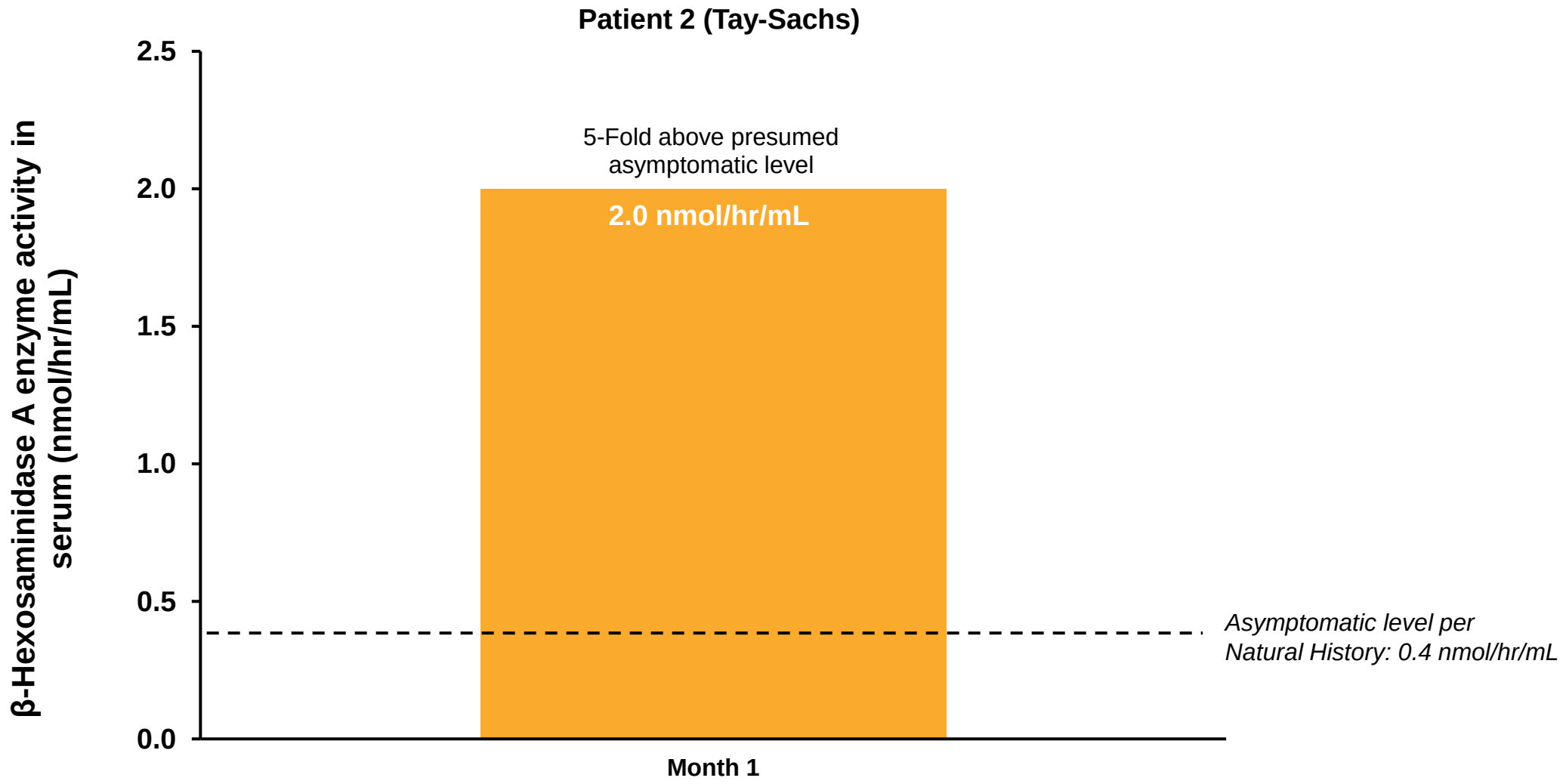
# Patient 2 (Tay-Sachs) experienced Hex A enzyme activity 25% of normal at Month 1

TSHA-101
GM2

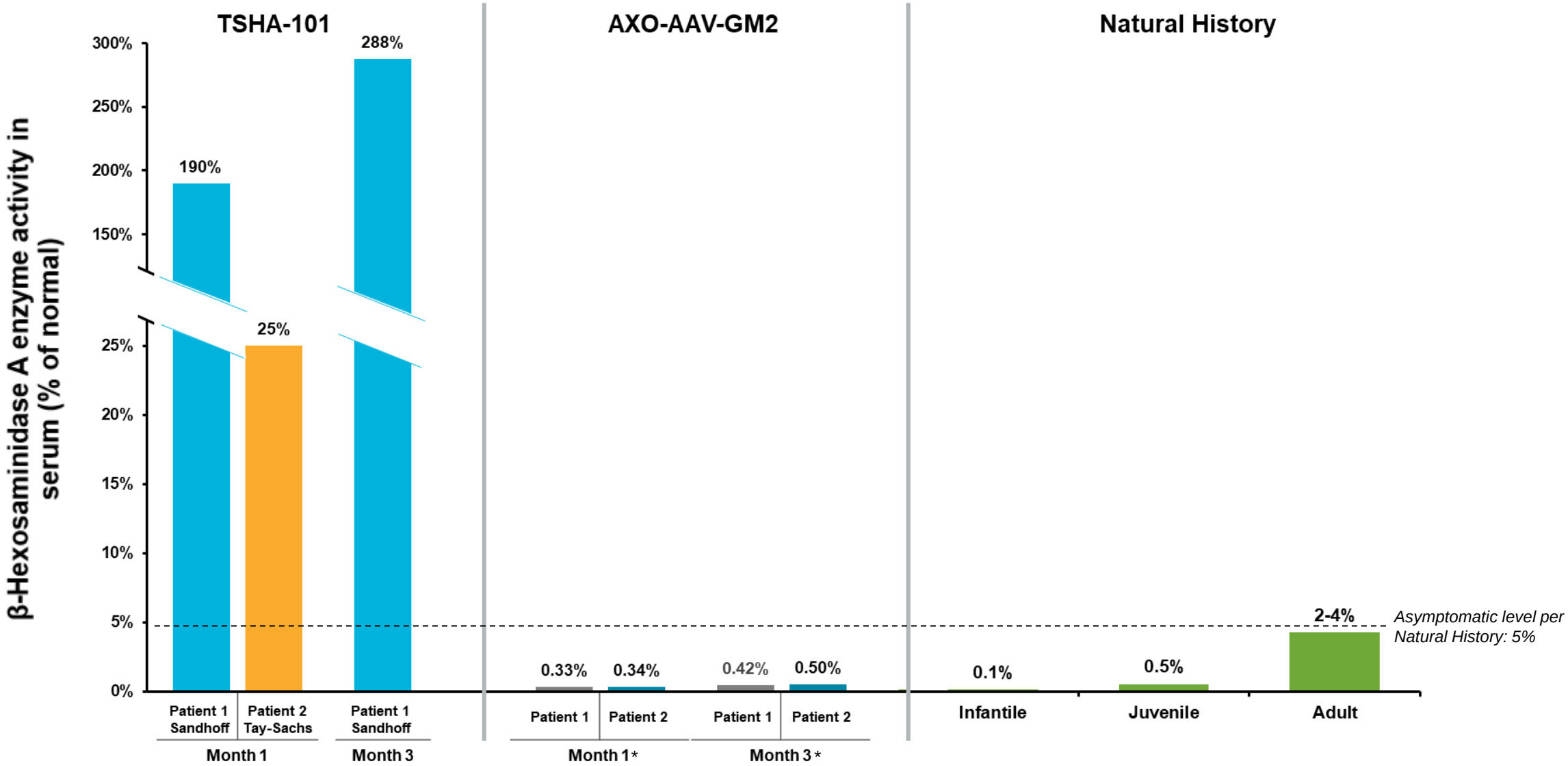


# Patient 2 (Tay-Sachs) experienced Hex A enzyme activity 5-fold above presumed asymptomatic level at Month 1

TSHA-101
GM2



# TSHA-101 Hex A enzyme activity compares favorably to competitive gene therapy program and natural history

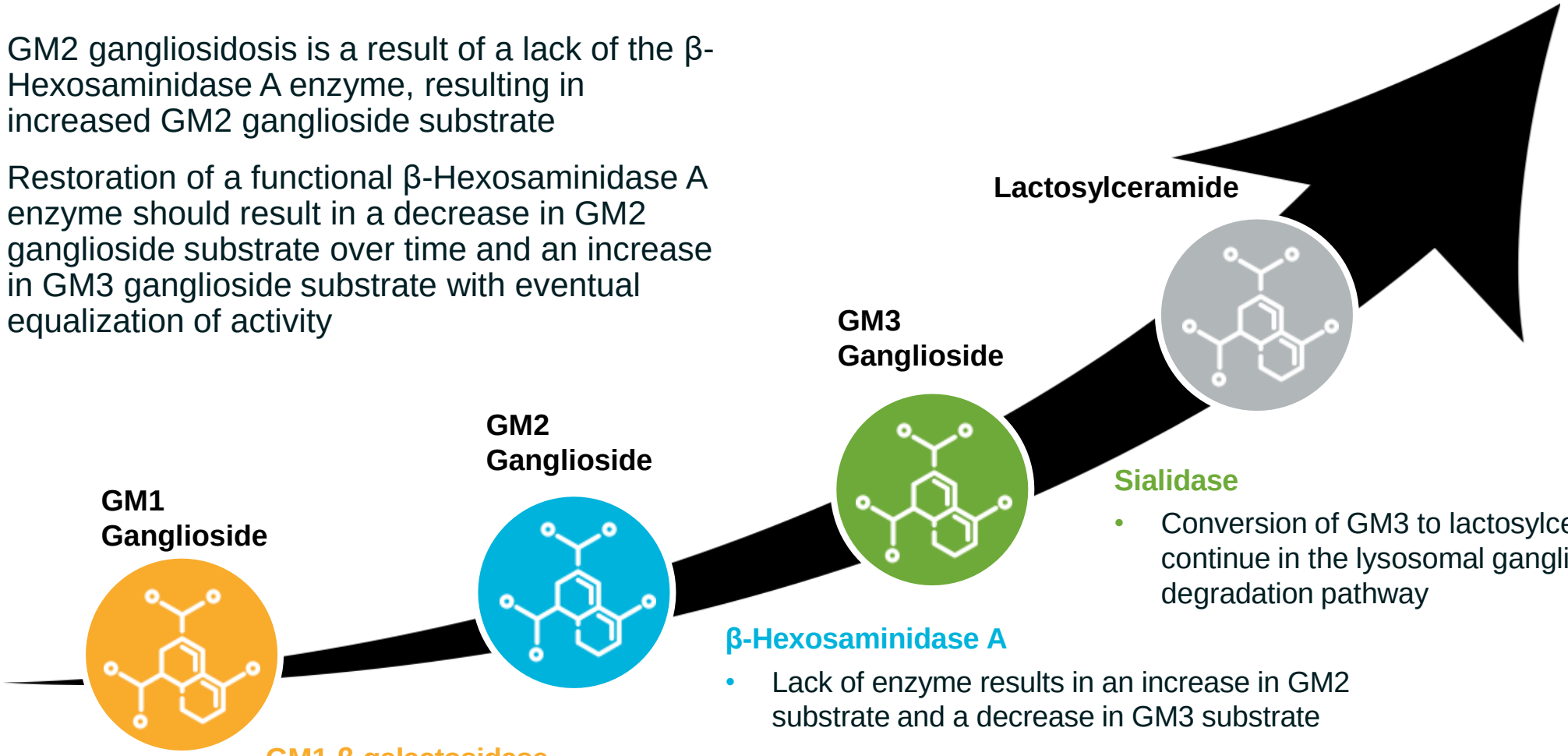



*Axovant Gene Therapies, Corporate Presentation - October 2019

# Metabolism of ganglioside substrates as a measure of functional Hex A enzyme activity

- GM2 gangliosidosis is a result of a lack of the β-Hexosaminidase A enzyme, resulting in increased GM2 ganglioside substrate
- Restoration of a functional β-Hexosaminidase A enzyme should result in a decrease in GM2 ganglioside substrate over time and an increase in GM3 ganglioside substrate with eventual equalization of activity

## Lysosomal Ganglioside Degradation




**Sialidase**

- Conversion of GM3 to lactosylceramide to continue in the lysosomal ganglioside degradation pathway

**β-Hexosaminidase A**

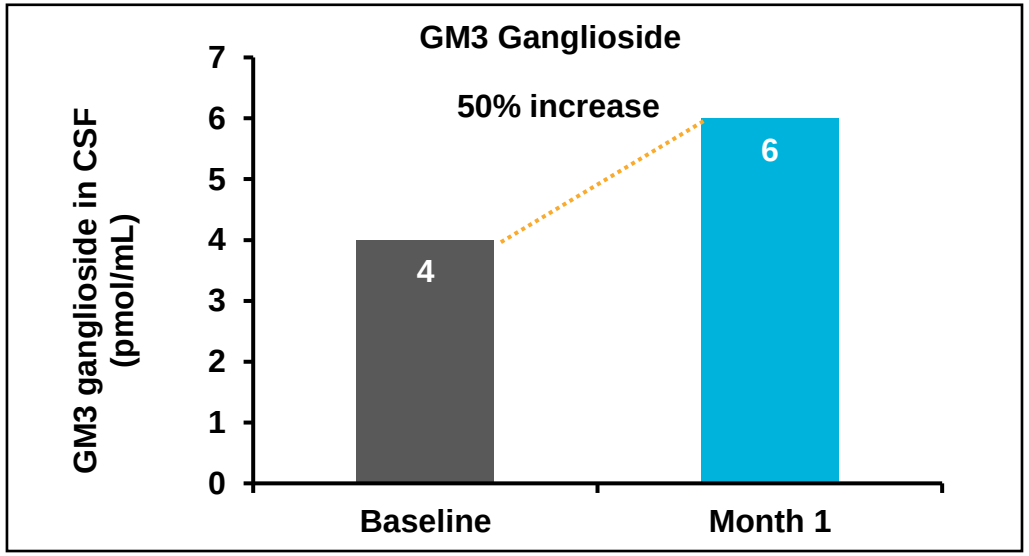
- Lack of enzyme results in an increase in GM2 substrate and a decrease in GM3 substrate

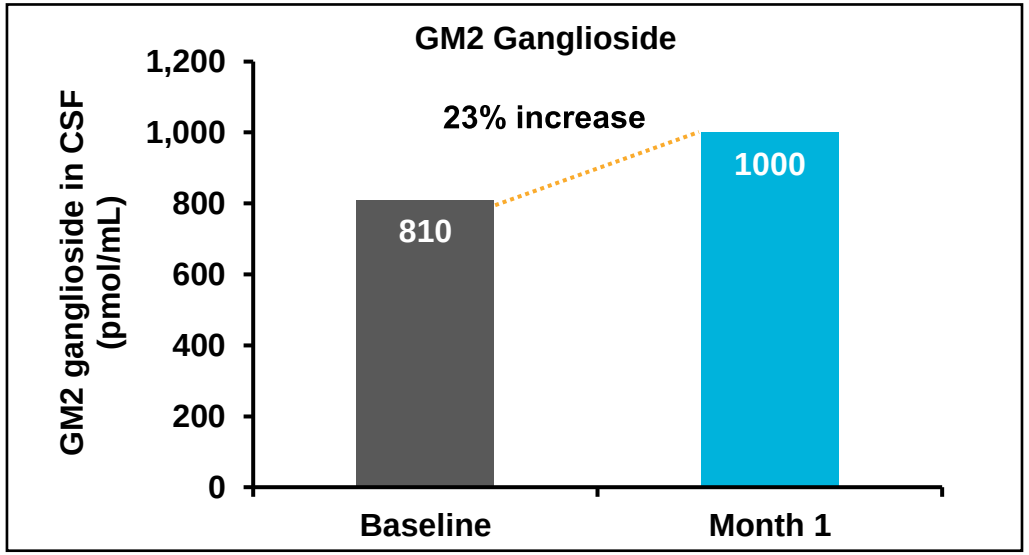
**GM1-β-galactosidase**

- Enzyme converts GM1 ganglioside to GM2 ganglioside

# Confirmatory evidence of pathway restoration by demonstrating conversion of GM2 to GM3 ganglioside in CSF

- In affected patients, GM3 levels remain consistently low over time due to blockage in metabolic pathway
- Substrate levels in Patient 1 (Sandhoff) demonstrated a greater rate of increase in GM3 ganglioside versus GM2 ganglioside in the CSF suggesting restoration of metabolic pathway and Hex A enzyme function
- GM3 ganglioside increased from baseline by 50%, a 2:1 ratio, demonstrating conversion of GM2 to GM3
- Normalization should happen over time



# Preliminary data suggest that TSHA-101 was well-tolerated with no significant drug-related events

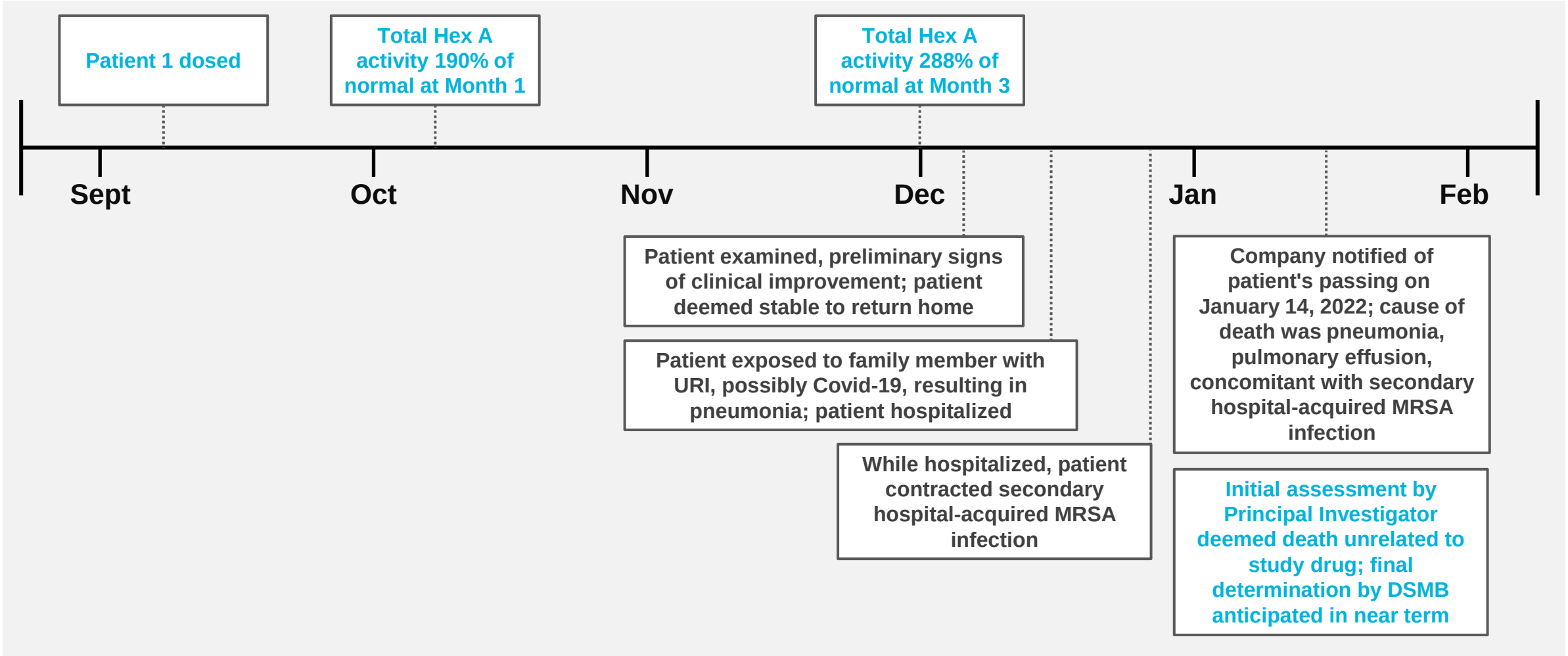
TSHA-101
GM2

- Pre-treatment AST elevations were observed in both subjects, with mild-to-moderate elevations noted after gene transfer

| Clinical Feature | Patient 1 (Sandhoff) | Patient 2 (Tay-Sachs) |
|---|---|---|
| **Related Treatment Emergent Adverse Events (TEAE)** | Mild elevations in liver function tests | Aspartate aminotransferase increased |
| **Related Serious Adverse Events (SAE)** | none | none |

# Upon returning home, Patient 1 (Sandhoff) unvaccinated was exposed to family member symptomatic for upper respiratory infection, possibly Covid-19 resulting in pneumonia

TSHA-101
GM2



# Positive initial biomarker data for TSHA-101, the first bicistronic gene therapy in history

TSHA-101
GM2

## Safety

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## GM2 to GM3 Metabolic Pathway

- Confirmatory evidence of pathway restoration with increased levels of GM3 ganglioside in CSF
- Patient 1 (Sandhoff) demonstrated a greater rate of increase in GM3 ganglioside versus GM2 ganglioside

# Anticipated next steps for TSHA-101

3 patients enrolled with 4th patient currently in pre-screening. Company plans to submit protocol amendment to expand target enrollment from 4 patients up to 15 patients

Resupply of drug completed to support study expansion

Additional clinical safety and efficacy data by YE 2022

# Focused on achieving anticipated near-term milestones in 2022 and building long-term value

**January:** GAN high dose and long-term safety and durability data
Preliminary clinical safety and Hex A enzyme activity data

**February:** Presentation of CLN7 preliminary clinical safety and efficacy data at WORLDSymposium

**H1 2022:** Clinical biomarker data for TSHA-118 in CLN1 disease

**YE 2022:** Preliminary clinical data for TSHA-102 in Rett syndrome
Clinical biomarker data for TSHA-105 in SLC13A5

# Thank you to our patients, caregivers, advocacy groups and collaborators

**Patients & Caregivers**

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